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DOCUMENT-IDENTIFIER: US 4462839 A
TITLE: Enteric coating for pharmaceutical dosage forms

Abstract Paragraph Left (1):
The application discloses a process for making a polymeric powder which is readily dispersible in water to provide a composition useful for forming an enteric coating on pharmaceutical dosage forms and also a process for using the powder for its intended purpose.

Brief Summary Paragraph Right (1):
This invention relates to a polymeric powder which is readily dispersible in water to make a composition useful for providing enteric coatings on pharmaceutical dosage forms such as tablets, pills, capsules, powders, granules and beads. More particularly, the invention relates to such a polymeric powder wherein very small spherical powder particles are aggregated together and when stirred in water with mild agitation readily break up and allow the individual particles to disperse. The invention also relates to a process for making such a powder and to a process for utilizing the same.

Brief Summary Paragraph Right (3):
Pharmaceutical dosage forms such as tablets and the like commonly consist of a core containing one or more pharmacologically active ingredients together with various excipients which serve as binding agents, disintegrants, etc. The core may be provided with some form of a coating which may serve a variety of purposes such as rendering the dosage more palatable, improving the appearance, controlling release of the active ingredient both as to time and place, and/or for ease of identification. Coatings which are insoluble in the gastric juices of the stomach but which dissolve in the alkaline environment of the intestines are known and are needed for a variety of medical reasons not germane to the present invention. Such coatings are variously referred to as enteric coatings or enterosoluble coatings and will be so referred to hereinafter.

Brief Summary Paragraph Right (8):
Presently known techniques for mechanical particle size reduction have not been successful in producing polymer particles of the preferred size range. There are known emulsion polymerization techniques for forming dispersions having particles of the desired size but these techniques leave potentially physiologically harmful residual monomer in the dispersion and are therefore not entirely satisfactory when the dispersion is to be used for coating pharmaceutical or food products. Moreover, the most desirable enteric coatings are composed of polymers such as cellulose acetate phthalate which are incapable of being emulsion polymerized.

Brief Summary Paragraph Right (9):
To avoid the problems associated with emulsion polymerization, aqueous polymer dispersions having the requisite particle size and form can be made by dissolving the polymer in a water immiscible organic solvent, and emulsifying the organic solution in water containing at least one nonionic, anionic or cationic emulsifying agent. The crude emulsion is then subjected to comminuting forces sufficient to form a colloidal or near colloidal dispersion of small, even sized spherical polymer particles having a diameter of less than 1.0 .mu.m, preferably between 0.2 and 0.5 .mu.m. The organic solvent is stripped from the system by distillation. For more details as to a process for making such a polymer emulsion or dispersion, reference is directed to U.S. Pat. No. 4,177,177 to Vanderhoff et al. The actual method of forming the dispersion is not a part of the present invention and methods other than that described in the Vanderhoff et al. patent may be used, so long as the desired polymer particle size and shape is obtained. U.S. Pat. No. 4,330,338 to Banker teaches the use of aqueous dispersions of various polymers including cellulose acetate phthalate for forming coatings on pharmaceutical dosage forms.

Brief Summary Paragraph Right (10):
Applicants have found that while aqueous dispersions of some polymers such as ethyl cellulose are chemically stable for relatively long periods of time, perhaps indefinitely, dispersions of cellulose acetate phthalate are not. The presence of water in the dispersion hydrolyzes the cellulose acetate phthalate and gradually increases the phthalic acid content to beyond acceptable limits for pharmaceutical use. This inability to successfully store cellulose acetate phthalate aqueous dispersions for long periods of time also applies for the same reason to aqueous dispersions of such other known enteric polymers as hydroxypropyl methylcellulose phthalate and polyvinyl acetate phthalate. Not being able to successfully store the polymer dispersion is particularly undesirable in view of the fact that the scale on which the dispersions are typically used is significantly smaller than the scale on which they can be economically manufactured.

Brief Summary Paragraph Right (13):
U.S. Pat. No. 2,800,463 to Morrison describes a process for converting an aqueous polyvinyl acetate emulsion containing emulsifying agents or protective colloids like polyvinyl alcohol, gum tragacanth, gum acacia, etc. into a powder capable of being redispersed in water. All of the protective colloids mentioned by Morrison are water soluble over a wide range of pH. As described, the process involves either spray drying or freeze drying. The spray drying is carried out at temperatures below that at which the polymer particles sinter together. Unlike the present invention, Morrison relies primarily on temperature control, rather than on a barrier material, to prevent polymer particle sintering, fusion or coalescence during spray drying. Additionally, if the Morrison protective colloids were used in quantities sufficient to prevent coalescence of enteric polymer particles during spray drying, the protective colloids would adversely affect enteric performance of films formed from the spray dried compositions. The dried powder is described by Morrison as being useful in various ways such as for manufacture of paint and adhesives. There is no suggestion that the powder be used to make a composition useful for coating pharmaceutical dosage forms and certainly no suggestion that the powder would be useful for enteric coatings.

Brief Summary Paragraph Right (14):
According to U.S. Pat. No. 4,112,215 to Boessler et al., a dry powder of a polymeric material suitable for use in a solvent coating composition for pharmaceutical dosage forms may be produced by spray drying an aqueous dispersion of certain vinyl copolymers. The spray drying is carried out at a temperature such that the vinyl copolymer particles do not exceed the minimum film-forming temperature of the polymer. This method requires very careful control of the temperature of the air in the spray dryer. As pointed out in said U.S. Pat. No. 4,112,215, the actual air temperature must be chosen depending upon the amount of water in the dispersion as well as upon the known film-forming temperature of the polymer. Other factors not mentioned in the patent but which affect the heating of the polymer particles are the temperature of the water in the dispersion and the size of the particles. As pointed out in the patent, the only way of knowing whether the proper air temperature is used is by examination of the product obtained after completion of the drying operation; obviously not a very desirable circumstance.

Brief Summary Paragraph Right (16):
The present invention achieves the basic goal of the invention of said copending application Ser. No. 440,118; namely, an enteric polymer is dry powder form capable of being readily dispersed in water to provide, with the addition of a suitable plasticizer, a composition useful for forming an enteric coating on pharmaceutical dosage forms. However, the physical composition of the powder of this invention is distinctly different from the powder of application Ser. No. 440,118, and the process of making the same is also distinctly different.

Brief Summary Paragraph Right (17):
According to the present invention, the aqueous dispersion of substantially spherical cellulose acetate phthalate particles of less than 5.0 .mu.m diameter, preferably of a diameter between about 0.2 .mu.m to 0.5 .mu.m, optionally formed as above described in reference to the patent to Vanderhoff et al. U.S. Pat. No. 4,177,177, is spray dried after having had added thereto a basic salt. As previously mentioned, the purpose of the powder formed by spray drying the dispersion is for redispersion in water to form a composition suitable for use in providing an enteric coating on pharmaceutical dosage forms. Unlike the invention of the Durand et al. U.S. Pat. No. 3,539,365, which uses a water soluble barrier material that does not render the polymer particles water-soluble, and unlike the invention of application Ser. No. 440,148, which uses a

water insoluble barrier material that does not render the polymer particles water-soluble, the present invention uses a water soluble material that also renders the polymer praticles partially soluble in water to minimize coalescense during the spray drying of the dispersion, such that redispersion is possible.

Brief Summary Paragraph Right (20):
When the pharmaceutical manufacturer is ready to use the powder for forming an enteric composition for coating tablets or the like, the powder is added to water, followed by the addition of a suitable plasticizer such as dibutyl sebacate, diethyl phthalate, tributyl citrate, triglycerylacetate, propylene glycol, castor oil, triacetin, polyethylene glycol or mixture of these or other pharmaceutically acceptable plastizers. The plasticizer is preferably used in an amount of between 10% and 40% by weight of the dry polymer. If desired, pigments, flavorings and/or preserving agents may also be added. Upon stirring, the aggregates break up to free the polymer particles in the form and near the size they had in the original dispersion. The water soluble portion or "skin" of the polymer particles serves as a dispersant enabling easy dispersion of the water insoluble polymer particles.

CLAIMS:

1. A process of making a polymeric powder which is readily dispersible in water to provide a composition useful for forming an entric coating on pharmaceutical dosage forms, comprising providing a freshly prepared aqueous dispersion of spherical water-insoluble enteric polymer particles, adding to said dispersion a phosphate salt in an amount sufficient to minimize coalescense of the particles during spray drying, thoroughly mixing, and spray drying to form the powder.

8. The process set forth in claim 7 comprising the additional steps of dispersing the spray dried powder in water, adding a plasticizer in an amount of between 10% and 40% of the weight of the dry polymer to form a coating composition, and coating a pharmaceutical dosage form therewith.

10. A process of making a polymeric powder which is readily dispersible in water to provide a composition useful for forming an enteric coating on pharmaceutical dosage forms, comprising providing a freshly prepared aqueous dispersion of cellulose acetate phthalate particles, adding to said dispersion a phosphate salt in an amount sufficient to minimize coalescense of the particles during spray drying, thoroughly mixing, and spray drying to form the powder.

17. The process set forth in claim 16 comprising the additional steps of dispersing the spray dried powder in water, adding a plasticizer in an amount of between 10% and 40% of the weight of the cellulose acetate phthalate particles to form a coating composition, and coating a pharmaceutical dosage form therewith.

19. A polymeric powder capable of being readily dispersed in water to provide with the addition of a plasticizer a composition useful for forming an enteric coating on pharmaceutical dosage forms, said powder consisting essentially of spherical water-insoluble enteric polymer particles, said enteric polymer particles having a water-insoluble core of such polymer and a water soluble surface portion of such polymer.